Why is Chromosome Segregation Error in Oocytes Increased With Maternal Aging?

It is well documented that female fertility is decreased with advanced maternal age due to chromosome abnormality in oocytes. Increased chromosome missegregation is mainly caused by centromeric cohesion reduction. Other factors such as weakened homologous recombination, improper spindle organization, spindle assembly checkpoint (SAC) malfunction, chromatin epigenetic changes, and extra-oocyte factors may also cause chromosome errors.

The oogenesis in mammals is a long and complicated process, characteristic of its two arrests and two consecutive meiotic divisions following DNA replication in S-phase. After replication, the homologous chromosomes pair by synapsis, and they recombine between the maternal chromatid and paternal chromatid in fetal ovaries. In most females of mammalian species, oocytes are all arrested at the diplotene stage of the first meiosis (meiosis I) prophase at birth, and continue to be arrested at this stage until puberty (38). The obvious hallmark for oocytes in this stage is a prominent vesicle-like nucleus in the central cytoplasm, which is named germinal vesicle (GV). In every estrus cycle of sexually matured females, the fully grown oocytes resume meiosis following the pituitary luteinizing hormone (LH) surge, manifested by GV breakdown (GVBD). Following meiosis resumption, the oocytes assemble the organized microtubules and condensed chromosomes into the metaphase I spindle, and then the oocytes emit half of the homologous chromosomes into the first polar body (reductional division) and complete meiosis I. Without DNA replication, the oocytes quickly enter the second meiosis (meiosis II), with the formation of metaphase II spindle containing the pairs of chromatids, and are arrested at the metaphase II stage (the second arrest) until fertilization. The oocytes release from the MII arrest and complete the meiosis II upon fertilization, during which the sister chromatids separation occurs (equational division) (19) (FIGURE 1). For humans, the oocytes could survive being arrested at prophase of meiosis I for as long as half a century.

It is worth wondering whether the oocytes are suffering deterioration during the lengthy wait and whether the fertility is largely exacerbated by maternal age. That is true. The risk of spontaneous abortion increases to ~75% among women over 40 years of age compared with only 12% among women aged <20 years (98). The chromosome abnormalities account for almost 50% of all the miscarriages (14), and aneuploidy explains 60% of the above chromosome-induced miscarriages. Human oocytes are highly prone to aneuploidy, which is the leading cause of pregnancy loss, birth defects, and mental deficiency. Aneuploidy is predominantly [80–90% (28)] and originated from the chromosome missegregation in meiosis I, e.g., 95% aneuploidy for trisomy 21 (5); and the incidence of aneuploidy is well associated with the maternal age (24, 25). For humans, the incidence of aneuploidy is 2% in their twenties, although it sharply skyrockets to 35% around 40-yr-old (25). So the increased chromosome segregation errors are well associated with the maternal age-related miscarriages. During maternal aging, the disorders or impairment of the mechanisms of chromosome segregation predispose the chromosome missegregation, especially in meiosis I, and leads to high rates of aneuploidy. For this topic, differences may exist between species: there is no increased aneuploidy in porcine oocytes since maternal aging (34) and oocyte aging do not contribute to age-related infertility in the cheetah (15). Here, we review the potential mechanisms, especially the molecular basis associated with increased chromosome missegregation with advanced maternal age, mainly based on studies in humans and rodents. The related factors are classified into two categories: intrinsic factors within oocytes and the extrinsic causes.

Intrinsic Factors

The Deteriorated Cohesion is the Leading Cause for the Age-Related Chromosome Missegregation

With completion of the synopsis (chromosome pairing) and reciprocal recombination, the visible homologous chromosomes in prophase-arrested oocytes exist as bivalents, each one comprising of a pair of homologous chromosomes linked by the chiasma, which is formed by sister chromatid
cohesion localizing at the chromosome arms. The sister chromatid cohesion, underpinning of the physical linkage, is critical for the maternal and paternal chromatids to separate to the two opposite poles (78). It is worth noting that the cohesions also localize at centromeres, where the sister chromatids are held together. In mammalian oogenesis, the sister chromatid cohesion is mediated by the multi-subunit protein complex called cohesin, consisting of the meiosis-specific subunits REC8, STAGE3, SMC1β, and SMC3 (20, 89, 94). During the metaphase-anaphase transition in meiosis I, the chiasmata are resolved through cleavage of the cohesin kleisin subunit Rec8 along chromosome arms by the separase-mediated proteolytic pathway (51), followed by the homologous chromosomes separation. As shown in FIGURE 2, the sister chromatid cohesins persist at centromeres and hold the sister chromatids together until anaphase occurs in meiosis II. The mechanisms underlying the protection of centromeric cohesion from separase cleavage when resolution of chiasmata occurs during meiosis I are emerging. The shugoshin 1 (124) and shugoshin 2 (58, 70) have been discovered to localize at the centromeres to protect Rec8 from cleavage and prevent precocious sister chromatid separation in meiosis I. The function of shugoshins in meiosis I is achieved by recruiting the PP2A (protein phosphatase 2A) to centromeres, and PP2A causes de-phosphorylation of Rec8 to counteract its cleavage-dependent phosphorylation. Although the shugoshin-PP2A interaction is only validated in yeast, the mechanisms may be prevalent in mammalian oocytes, at least, the study on crystal structure of the complex of a human shugoshin 1 fragment and AB’C PP2A (a kind of PP2A, named according to its composing of A, B’, C subunits) gives the cue (123).

In view of the long span for the chiasmata maintenance in prolonged-arrested oocytes, the cohesions have been considered as the major cause for the increased chromosome missegregation including aneuploidy in oocytes with advanced maternal age (6, 25, 67, 87, 122). The hypothesis is elucidated in oocytes of Drosophila with impairment of sister chromatid cohesion by weak ORD (orientation disruptor, meiotic cohesion protein in Drosophila) mutant (41, 103) or SMC1 heterozygosity (102): the gradual deterioration of cohesion in the two models both lead to increased frequencies of homolog nondisjunction. The early hint in mammalian model comes from the SMC1β-deficient female mice, in which the cohesion loses as the maternal mice age, associating with increased chromosome abnormalities in meiosis I (27, 92). Recent studies

![Diagram of oocyte maturation process](http://physiologyonline.physiology.org/)

**FIGURE 1. Schematic figures of oocyte maturation process in most mammals**
GV arrest, the oocytes with germinal vesicle (GV) are arrested at the prophase of meiosis I at birth and last for as long as 50 yr until menopause in women. GVBD, GV break down; MI, metaphase I; AI, anaphase I; MII, metaphase II; Fertilization, oocyte fertilizing with the sperm; Zygote, female pronucleus (black) and male pronucleus (red) appeared at this stage.
explored that the weakened centromere cohesion and/or the sister chromatid cohesion is the initial cause for the increasing chromosome segregation errors in oocytes as maternal aging in two different but similar mouse models (natural aging mouse model and long-lived mouse model, respectively) (13, 63), and the phenomenon caused by cohesion loss may be magnified by shugoshin 2 reduction from the centromeres. In the natural aging mouse model, 90% aneuploidies in oocytes from old mice (16- to 19-mo-old, corresponding to 38- to 45-yr-old women) are related to weakened centromere cohesion, mainly resulting in separated sister chromatids and aneuploidy with single chromatids; that is similar to the case in human MII-arrested oocytes with advanced maternal age (87, 113).

The above model is actually established on two hypotheses: first, there is no turnover or replenishment of cohesion, at least no cohesion reloaded to the centromeres and the chromosome arms in oocytes with maternal aging. Second, the bivalents possessing cohesions have been constituted in the early premeiotic stages. Actually, there is no significant difference in the amount of total Rec8 between oocytes from the young and old mice in the natural aging mouse model, whereas the difference is that the chromosome-associated Rec8 reduces in oocytes from old mice (13). Concomitant with this, by creating mice whose Rec8 can be cleaved by the TEV (the tobacco etch virus) protease and transgenic mice whose intron 1 in Rec8 is inserted into a stop codon that is flanked by two loxP sites, combining with the TEV protease microinjection and ZP3-Cre transgenic mice, Tachibana-Konwalski et. al. demonstrate that there is little or no cohesion turnover during the growing phases in mouse oocytes, implying that gradual loss of cohesions without replenishment may attribute to the age-related aneuploidy (43, 107). For the second hypothesis, depletion of SMC1β in early prophase I stage during embryogenesis through conditional knockout method by the GDF-9-driven Cre recombinase, which functions in oocytes at primordial follicle stage to cut off the SMC1β gene flanked by two loxP sites, shows that SMC1β-mediated cohesions are established in initial meiotic stages and could satisfy their roles in subsequent meiotic processes (43, 93).

In conclusion, the cohesions are established in the embryonic premeiotic phase, and there is no or little efficient replenishment for the cohesions during the growing phase in oocytes, so when the cohesion amount declines to under a threshold level (13, 63) with maternal aging, this will cause increased chromosome segregation errors and aneuploidy in mouse oocytes.

Aberrations in Spindle Organization are Associated With Age-Related Abnormal Chromosome Segregation

In oocytes, proper segregation of chromosomes is dependent on their attachment to the spindle microtubules and correctly aligned at the spindle equator, so the formation of an integrated, stable meiotic bipolar spindle is the key to the chromosome segregation. The spindle malformation is accompanied with failure in chromosome congression and subsequent missegregation. Early studies showed high frequencies of abnormal MI and MII spindles as well as chromosome congression failure in oocytes from older women compared with those from young women (8, 115). The disrupted MI and MII spindles and chromosome misalignments are also found in the senescence-accelerated mice (SAM), which show age-associated defective meiotic events (66, 68). Miao et. al. summarize the morphologically abnormal spindles in aged oocytes (77). The exploration of gene expression profile in oocytes demonstrates that some genes involved in spindle assembly such as *Numa1*, Ran, and Tpx2 are mis-expressed in mouse old oocytes (85); a similar phenomenon appears in human oocytes, e.g., downregulation of *Docr1* (deleted in oral cancer 1 related) in old oocyte, which is responsible for spindle organization (21). The impaired spindle formation and its malfunction may be resulted from dysfunction of mitochondria (114) as maternal aging. Despite the relativity, there is lack of direct evidence to link the malformed spindle to increased chromosome missegregation, and time-lapse live imaging of fluorescein-tagged tubulin and chromosome dynamics during oocyte maturation may provide direct evidence.

Improper Recombination Established in Fetal Ovary May Create the Rudimentary Hidden Trouble for Late Chromosome Missegregation in Adults

In the “two-hit” hypothesis (9, 54, 119) for aneuploidy, improper recombinations, displayed as abnormal chiasmata when visible, formed in the fetal life (the first hit) are the footstone (53, 54), which makes it prone to chromosome missegregation under induction by kinds of influences in adult life (45), and the influences might accumulate or aggravate with maternal age. Lamb et. al. report the strong association between recombination alterations and human trisomies (55), and the number and site of recombination affect the accurate chromosome segregation in meiosis I of oocyte in human (24) or mouse (97). As for the relationship between recombination and age-related aneuploidy in humans, the data are mainly from human trisomy 21. The risky patterns of recombination for...
human trisomy 21 include no recombination, an exchange near the centromere, or a “crossover” close to the telomere. For the trisomy 21 from meiosis I, decreased frequency of susceptible recombination (near the centromere or telomere) occurs during maternal aging, and the reason is that there is no, if any, ability of older oocytes to resolve the poor recombinations (55, 56, 97).

Based on the animal models, investigators have explored some possible molecular bases for the
age-related, recombination-caused chromosome missegregation. The synaptonemal complex facilitates in the synapsis and subsequent reciprocal recombination. SYCE2 (synaptonemal complex central element) is required for synapsis and recombination (9). Deficient synaptonemal complex protein 3 (SCP3) in mice causes age-related embryonic lethality, which mainly comes from the aneuploidy in the oocytes (126). The mice with mutant Rad51c (responsible for DNA repair) also display failures in recombination and aneuploidies (52). The picture depicting the relationship of improper recombination and aneuploidy is set up in human oogenesis; however, the molecular mechanism is little known due to the lack of a proper animal model.

**Spindle Assembly Checkpoint is Still the Bone of Contention for the Age-Related Aneuploidy**

In mitosis, the accurate chromosome segregation during metaphase-to-anaphase transition depends on the proper chromosome congression in the metaphase equator with tense attachment between the chromosome kinetochores and spindle microtubules (80). Congression failure, even one chromosome off the metaphase plate, could be sensed by the surveillance system-spindle assembly checkpoint (SAC), which can prevent the anaphase from happening until all the chromosomes are correctly aligned at the metaphase plate of the bipolar spindle. So, the SAC plays a pivotal role in the chromosome segregation and aneuploidy prevention in mitosis (FIGURE 3).

The main SAC proteins include mitotic arrest-deficient (Mad) 1, Mad2, BubR1 (Mad3), budding uninhibited by benzimidazole (Bub) 1, Bub3, and Mps1. Previous studies reported that the SAC was absent in mammal oocytes, and this conclusion was mainly from the XO female mice with only a single X chromosome, in which most oocytes initiate the metaphase-anaphase transition even though the X chromosome univalent fails to align at the metaphase plate, resulting in aneuploidy inevitably (37, 60) (FIGURE 3C). In recent years, the main SAC proteins have been identified to exist and regulate the accurate segregation of homologous chromosomes and/or sister chromatids in mouse oocytes (FIGURE 3, A AND B); Mad1 regulates the chromosome congression during oocyte maturation (129); Mad2 affects the chromosome segregation in meiosis I (30–33, 83, 120) and meiosis II (47); Bub1 prevents chromosome segregation errors and aneuploidy (10, 125) in meiosis I in in vitro experiments, and the in vivo studies also show that heterozygous mutation of Bub1 in mouse (59) or conditional knockout of Bub1 specifically in mouse oocytes (76) both result in aneuploidy, mainly from meiosis I and also from the precocious separation of sister chromatids; Bub3 is required for correct separation of both the homologous chromosomes and sister chromatids in meiosis I and meiosis II, respectively (62); BubR1 regulates the chromosome alignment and meiotic progression in oocyte maturation (29, 121); Mps1 is required for the meiotic progression and chromosome segregation in mouse oocytes (23). However, we still could not bypass the question arising from the XO female mice, and two hypotheses have been proposed: 1) the SAC in oocytes is less stringent, allowing abnormal chromosomal behavior; 2) the univalent can mimic the bivalents to form bipolar attachments to escape SAC’s surveillance.

Several studies have reported that the transcripts or proteins of main SAC components change with oocyte aging in vitro or with maternal aging, accompanied by the increased incidence of chromosome missegregation. The expression of Mad2 protein is reduced in porcine oocytes while aging in vitro (73); similarly, the Mad2 transcripts decreased in mouse oocytes with post-ovulatory aging (101). The global analysis of transcripts in oocytes from old and young mice showed that the transcripts of SAC proteins (BubR1 and Bub1) decrease with aging and are associated with the increased aneuploidy (85); similar observations are found in human oocytes (99, 100). Loss-of-function experiment shows mutant of Bub1 induced chromosome missegregation in meiosis I of mouse oocytes, and the effect advanced during maternal aging. Similarly, knockout of BubR1 in mice leads to advanced aging with inescapable deficient...
chromosome separation and infertility (7). It is intuitively appealing that the SAC participates in the age-related chromosome segregation errors based on the above facts, as discussed by others (45, 75, 114), but there is no direct evidence to connect the disturbance of SAC to the increased aneuploidy with maternal aging. Using the reproductively aging mouse model in which the SAC is impaired (85), Duncan et. al. report that the deteriorated SAC is not the primary cause of increased chromosome missegregation associated with advanced maternal age (17). Consistent with this conclusion, Lister et. al. report that SAC function is not compromised in oocytes of aged mice (63) (FIGURE 3D). Fortunately, a newly published paper might give hints to the underpinning of the attracting puzzle. That is, the SAC-mediated cell-cycle control is specific in oocytes and could be satisfied only when a mass of but not all of the chromosomes attached to the bipolar spindle (81). The new data further support the first hypothesis to explain the SAC function in XO female mice. More important is that the picture might be imagined: the reduced expression of SAC proteins with advanced age may aggravate the susceptibility of oocytes to chromosome missegregation. The conflict might be reconciliated based on the fact that only when the SAC proteins are reduced, or the SAC system is impaired, below a threshold level will the effect emerge.

**Histone Modification Changes Correlate With the Failures in Chromosome Segregation While Aging**

Histone modification, particularly histone acetylation, phosphorylation, and methylaiton, is widely present in mammalian oocytes, and their existence as well as change are differently dependent on the modification types, residues, and species, including mouse (3, 46, 49, 82, 84, 96), swine (11, 18, 22, 86, 106, 116, 117), cattle (74, 91), sheep (35, 108), and human (90). The situation of the histone modification, especially acetylation, has been reported to be associated with oocyte aging or maternal aging. The levels of acetylation in several residues increased with postovulatory aging (36) or maternal aging (4, 104). The histone acetylation may regulate chromosome segregation based on the facts that the hyperacetylation induced by TSA leads to defective spindles and chromosome missegregation in oocytes of mouse (16) and swine (117) and that deacetylation failure induces aneuploidy in mouse oocytes (4). So the histone modification might be one of the links of increasing chromosome segregation and maternal aging, and a recent paper supports the hypothesis that the aging-associated defects in histone deacetylation are significantly correlated with chromosome missegregation in human oocytes (111). The data until now is far from determining that age-associated

![FIGURE 3. Schematic figure illustrating that the SAC might be involved in the increased chromosome missegregation as maternal aging](http://physiologyonline.physiology.org/)

A: normally, when the homologs align at the metaphase equator, the SAC is turned off, followed by anaphase and homologous chromosomes segregation. B: if chromosomes fail to align at the equator (congression failure), the SAC is kept active, which inhibits anaphase initiation. C: special cases are XO mice and Mlh1 mutant female mice. In these two kinds of mice, oocytes initiate anaphase and complete homologues separation even though not all the chromosomes are aligned at the metaphase plate, which is one univalent (for XO oocytes) or several univalents (for Mlh1 mutant oocytes) off the metaphase equator. D: weakened SAC as aging might ignore the misaligned chromosomes and initiate anaphase, causing aneuploidy. Arrowhead indicates the segregation of homologous chromosomes into one cell, and the chiasma is dissected probably due to cohesion loss. That the control of cell cycle by SAC in oocytes is less stringent by nature, combined with reduced expressive SAC proteins as maternal aging, makes the SAC an important, although still controversial, candidate for controlling age-associated chromosome missegregation.
histone modification changes contribute to increased chromosome segregation errors.

**Telomere: Is It True Beyond the Mouse Model?**

The telomere regulates the somatic cell aging by its shortening. In oocytes, telomere shortening is mainly caused by the reactive oxygen species (69), which increases during maternal aging. Experimental telomere shortening induces impaired chiasmata and synopsis, even abnormal spindles and chromosome misalignment (64, 65). It is worth noting that the cohesin component SMC1β is required to prevent the telomere shortening in mouse oocytes (2). The hypothesis needs to be tested in natural aging animal model and importantly in studies on human oocytes.

**TGF-β Signaling Pathway: It Remains at Hypothesis Stage**

The Smα/Mab pathway is an important transforming growth factor-β (TGF-β) signaling pathway (72). The issue comes from a recent study in the famous worm *Caenorhabditis elegans* (71). Mutations of TGF-β SMA/Mab delay the decline of age-related events including chromosome missegregation in the worm and better maintain their reproductive span. Intriguingly, the upregulated genes in the mutants can be found in the list of genes downregulated in mammalian oocytes with advanced age, e.g., SMC, Bub1, and Bub3. The observations indicate that conservative mechanisms may underlie the age-related decline of female reproductive capacity between worms and human. The effects of the TGF-β pathway on chromosome segregation might indirectly come from its effect on the early folliculogenesis in mice (109). To explore the functions of the TGF-β signaling pathway, its detailed roles in oogenesis and folliculogenesis need to be unveiled.

**Extrinsic Factors**

**Endocrinological Micro-environment Affects Chromosome Segregation in Oocytes**

Oocyte development indispensably depends on the complicated communications with its microenvironment, including the effects of hormone from surrounding cumulus cells; and the hormonal influence on the follicles indirectly affects their containing oocytes. Subtle alternations in hormonal regulation of follicle growth, which develop with maternal aging, lead to chromosome congression failure in the meiosis I, foreshowing the errors in chromosome segregation. The obvious example is the *LhbCtp* (an altered LH gene) transgenic female mouse, in which the LH hypersecretion changes the endocrine environment and causes high rates of congression failure in oocytes at MI and MII stages (26). In in vitro maturation, high concentration of FSH also impairs the chromosome alignment during meiosis I in mouse oocytes, resulting in high aneuploidy (95). Another identified crucial endocrine pathway relating to chromosome segregation in oocytes is the insulin signaling pathway. Glycogen synthase kinase-3 (GSK3) is the terminal enzyme in the insulin signaling pathway. Inhibition of GSK3 directly (118) or indirectly by long-time exposure of preantral follicles to insulin (1) results in the high incidence of homologue missegregation. Controversially, a recent study in *C. elegans* shows that a compromised insulin signaling pathway in the mutants could suppress the chromosome missegregation to increase with age, whereas the rate of chromosome segregation errors in mild-type worms increases with maternal aging (71). Based on the conservation of the insulin signaling pathway from worms to humans, we may speculate that it may function similarly in human reproduction regulation. Although it is known that endocrinology factors may play important roles in chromosome segregation during oocyte meiosis, we need to further explore whether their functions are direct or whether they indirectly affect oocytes, as well as what their effective proteins are.

**Environmental Factors Affect Chromosome Segregation Mainly Through Impeding Normal Physiological Status**

Environment is an indispensable factor in mammalian female reproduction. During the long reproductive span, females may suffer from pollution (especially the endocrine disruptors) in air, water, earth, food, and so on, affecting the chromosome segregation in oocytes and fertility. The incidence is higher with the poisonous material accumulating during maternal aging. Bisphenol A (BPA) is a typical endocrine disruptor and it is a man-made substance existing in our ordinary life, which is widely used in polycarbonate plastics and epoxy resins manufacturing and production of cans containing food, beverages, and dental sealants (79). The possible relationship between female meiotic defects and BPA was found accidentally based on the observation of the sudden increase of meiotic abnormalities, including aneuploidy, in oocytes from mice exposed to damaged plastic caging materials (39). Subsequent studies show that BPA could not only impair the final stages of oocyte maturation (12, 39) but also affect the developing ovaries in pregnant mice by disrupting ERβ (estrogen receptor β), resulting in compromised synopsis and recombination in fetal ovary as well as aneuploid eggs (105). Further research manifests that the maternal exposure to BPA leads to great changes in gene expression in fetal ovaries (57). In vitro studies also show that exposure to BPA for
mouse cumulus-oocyte complexes or follicles leads to spindle abnormalities and chromosome missegregation in mouse oocytes (12, 61). The screen in developed countries showed that BPA existed in kinds of body fluids in humans, including high levels in some placental and amniotic fluid samples, which may come from contaminated food, beverages, air, water, or soil (112). BPA is an endocrine disruptors, as mentioned, and there are other similar substances existing in our environment; the troubling thing is that their severe hazard in low doses may be ignored by the governmental guidelines based on the improper detection method, even in developed countries (40). BPA is just an example; more work needs to be done to detect similar environmental materials and to protect people from contamination.

**Lifestyle Habits are Positively Related With Abnormal Chromosome Behaviors in Oocytes**

In IVF clinic practice, lifestyle habits, especially cigarette smoking of men, women, or both, are important adverse factors (50, 127). For women, defects in chromosome segregation and aneuploidy in oocytes is one of the main outcomes from cigarette smoking. It is reported that there is a high frequency of diploid oocytes produced by inhibition of the first polar body formation in smokers (88, 128). To explore the effects of cigarette smoking on female fertility and oocyte quality, Jennings et. al. (42) employed a model of mice whose lungs received cigarette smoke directly for 12 wk and found disorganized spindle and chromosome segregation failure in oocytes from smoking mice, indicating chromosome missegregation. As for the effect of alcohol use on IVF outcomes, it is not quite certain because of a scarcity of evidence (50). However, studies showed that alcohol, as a “spindle-active” substance, contributes to microtubule and spindle instability, resulting in chromosome missegregation (48, 110). It is easily imagined that the effects of lifestyle habits accumulate during maternal aging, although there is a lack of direct evidence.

**Conclusions**

The discussions of increased chromosome missegregation with advanced maternal age seem to be based on the hypothesis that there is no capacity to produce oocytes for the mammalian females at birth but saying nothing of adults. Although recent studies report the existence of germline stem cell in mice of different ages (neonatal, juvenile, and adult) (44, 130), the well documented risk factor of maternal age in human aneuploidy likely goes against the existence of the stem cell in human ovaries. The paradox might result from the fact that there are no stem cells in human ovaries, whereas there are in mouse ovaries, just like the

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**FIGURE 4.** Cartoon outlining the intrinsic and extrinsic factors involved in advanced chromosome missegregation in oocytes as maternal aging

There are three stages that are vulnerable in mammalian oogenesis: 1) synapsis and recombination established in fetal ovary, 2) following follicle formation that also occurred in fetal ovary, 3) oocyte growth and meiotic maturation completed in adult ovary. The factors related to each stage are cataloged based on the evidence so far, but the classification is not absolute. The outcomes of “chromosome segregation error” occur in the stage “oocyte growth and maturation,” so the consequences from the factors involved in the two early stages should be displayed in the last stage. Vice versa, the effects of factors classified into the last stage may be the accumulating outcomes from the early stages, and cohesion deterioration is an obvious example.
differences of aneuploidy rates between the two species (very low in normal mouse oocyte).

Based on the above discussions of the possible molecular mechanisms underlying the age-related chromosome missegregation, especially on the recently published papers about cohesion involvement in chromosome segregation, the enigmatic Mona Lisa smile begins to be unveiled slightly. To our knowledge, the age-associated chromosome missegregation is the result of all kinds of causes, and they affect chromosome segregation in different stages during oogenesis (FIGURE 4). So far known is that the centromeric cohesions may constitute the key factor contributing to the regulation of “age-dependent chromosome segregation.” Less stringent SAC by nature deteriorates during advanced maternal age and further promotes chromosome segregation failures. As for the causes of “telomere” and “recombination,” they might tangle with the cohesion mechanism. Although reported, little functional details of histone modification or TGF-β have been explored. Some causes are exogenous, e.g., endocrinological and environmental factors, and both are also important in determining proper chromosome segregation, which may influence the folliculogenesis and initiate the original causes for subsequent catastrophe.

Numerous recent studies utilize proper technologies and animal models to explore the molecular basis for the age-related chromosome missegregation, and they show convincing data. The technologies and methods include conditional knockout of a specific gene in mouse oocytes by GDF9- or ZP3-driven Cre recombinase (85, 98), the TEV protease cleavage system (107), and gene mutant mice (81). The natural aging mouse model (13) and a long-lived wild-type mouse model (63) are also used. The utilization of these methods and models in future studies should broaden and deepen the discoveries about the relationship between increased chromosome segregation errors and maternal aging.

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